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(54) Title: QUINOLINE-4-CARBOXAMIDE DERIVATIVES AS NK-3 AND NK-2 RECEPTOR ANTAGONISTS

(57) Abstract: Certain compounds of formula (I) below or a pharmaceutically acceptable salt or hydrate thereof: (I) wherein: R_1 is H or C_{1-6} alkyl; R_2 is aryl or C_{3-7} cycloalkyl or heteroaryl; R_3 is H or C_{1-3} alkyl, optionally substituted by one or more fluorines; R_4 is R_8R_9; R_8 is a single bond, C_{1-6} alkyl, or aryl; R_9 is H, COO R_{10}, or N $R_{11}R_{12}$; R_{10} is H or C_{1-6} alkyl; R_{11} and R_{12} are independently selected from H and C_{1-6} alkyl; R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, aryl, or a single or fused ring aromatic heterocyclic group; R^6 represents H or up to three substituents independently selected from the list consisting of: C_{1-6} alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, amino or mono- or di-C_{1-6} alkylamino; R_7 is H or halo; a is 1-6; and any of R_2, R_5, R_8, R_{10}, R_{11} and R_{12} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo; a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds and composition in medicine.

QUINOLINE-4-CARBOXAMIDE DERIVATIVES AS NK-3 AND NK-2 RECEPTOR ANTAGONISTS

The present invention relates to novel compounds, in particular to novel quinoline derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

The mammalian peptide Neurokinin B (NKB) belongs to the Tachykinin (TK) peptide family which also include Substance P (SP) and Neurokinin A (NKA). Pharmacological and molecular biological evidence has shown the existence of three subtypes of TK receptor (NK_1, NK_2 and NK_3) and NKB binds preferentially to the NK_3 receptor although it also recognises the other two receptors with lower affinity (Maggi et al, **1993**, *J. Auton. Pharmacol., 13*, 23-93).

Selective peptidic NK_3 receptor antagonists are known (Drapeau, **1990** *Regul. Pept.*, 31, 125-135), and findings with peptidic NK_3 receptor agonists suggest that NKB, by activating the NK_3 receptor, has a key role in the modulation of neural input in airways, skin, spinal cord and nigro-striatal pathways (Myers and Undem, 1993, *J.Physiol.*, 470, 665-679; Counture et al., 1993, *Regul. Peptides*, 46, 426-429; Mccarson and Krause, 1994, *J. Neurosci.*, 14 (2), 712-720; Arenas et al. 1991, *J.Neurosci.*, 11, 2332-8). However, the peptide-like nature of the known antagonists makes them likely to be too labile from a metabolic point of view to serve as practical therapeutic agents.

International Patent Application, Publication number WO 00/31037 discloses certain compounds stated to be non-peptide NK-3 antagonists and also to have NK-2 antagonist activity. These compounds are disclosed to be of potential use in the prevention and treatment of a wide variety of clinical conditions which are characterised by overstimulation of the Tachykinin receptors, in particular NK-3 and NK-2.

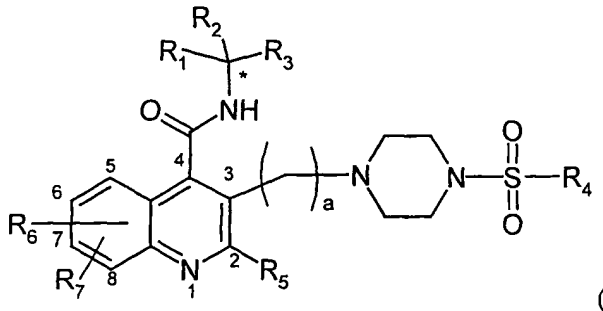
We have now discovered a further novel class of potent non-peptide NK-3 antagonists some of which fall within the generic scope of WO 00/31037. The new compounds are also far more stable from a metabolic point of view than the known peptidic NK-3 receptor antagonists and are of potential therapeutic utility. The new compounds also have good NK-2 antagonist activity and are therefore considered to be of potential use in the prevention and treatment of a wide variety of clinical conditions which are characterised by overstimulation of the Tachykinin receptors, in particular NK-3 and NK-2.

These conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity, cough; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjuctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systhemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders; increased blood pressure, proteinuria, coagulopathy and peripheral and cerebral oedema following pre-eclampsia in pregnancies (hereinafter referred to as the 'Primary Conditions').

Certain of these compounds also show CNS activity and hence are considered to be of particular use in the treatment of disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntington's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of the blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine, (hereinafter referred to as the 'Secondary Conditions').

The compounds of formula (I) are also considered to be useful as diagnostic tools for assessing the degree to which neurokinin-3 and neurokinin-2 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms.

According to the present invention, there is provided a compound of formula (I) below or a pharmaceutically acceptable salt or hydrate thereof:



(I)

(I)

wherein:

R_1 is H or C_{1-6} alkyl;

R_2 is aryl or C_{3-7} cycloalkyl or heteroaryl;

R_3 is H or C_{1-3} alkyl, optionally substituted by one or more fluorines;

R_4 is R_8R_9;

R_8 is a single bond, C_{1-6} alkyl, or aryl;

R_9 is H, COO R_{10}, or N $R_{11}R_{12}$;

R_{10} is H or C_{1-6} alkyl;

R_{11} and R_{12} are independently selected from H and C_{1-6} alkyl, or are joined to form a 5-7 membered heterocyclic ring;

R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, aryl, or a single or fused ring aromatic heterocyclic group;

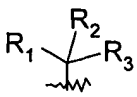
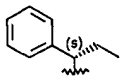
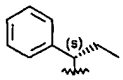
R_6 represents H or up to three substituents independently selected from the list consisting of: C_{1-6} alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, amino or mono- or di-C_{1-6} alkylamino;

R_7 is H or halo;

a is 1-6; and

any of R_2, R_5, R_8, R_{10}, R_{11} and R_{12} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo;

subject to the proviso that said compound is not a compound of formula (I) wherein R_7 represents H, R_6 represents H, R_5 represents phenyl, a is 1, and R_1, R_2, R_3 and R_4 are one of the following combinations:

	R_4
	$-NH_2$
	

Advantageously, R_3 represents methyl or ethyl or iso-propyl.

Suitably, R_2 represents phenyl or cyclohexyl.

Preferably, R_1 is hydrogen.

Suitably, R_5 is unsubstituted phenyl.

Optionally, each of R_6 and R_7 may represent hydrogen.

In preferred embodiments, a is 1-3. Most preferably, a is 1.

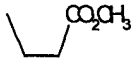
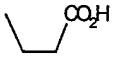
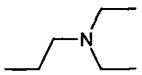
Advantageously, R_8 is methyl, ethyl or phenyl. In especially preferred embodiments, R_8 is methyl. In other preferred embodiments, R_8 is phenyl.

In some embodiments, R_9 is H.

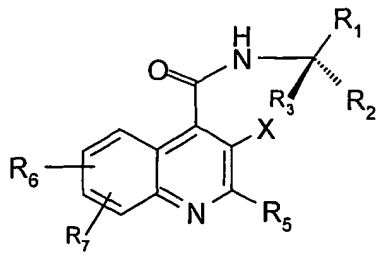
In other embodiments, R_9 is $COOR_{10}$ and R_{10} is H or methyl or ethyl.

In yet other embodiments, R_9 is $NR_{11}R_{12}$, and R_{11} and/or R_{12} is methyl, ethyl or propyl. Suitably, each of R_{11} and R_{12} is the same one of ethyl or propyl.

In particularly preferred embodiments, a is 1, R_6 is H, R_1 is H, R_5 is unsubstituted phenyl, R_7 is hydrogen, and R_2, R_3 and R_4 are selected from the following combinations:

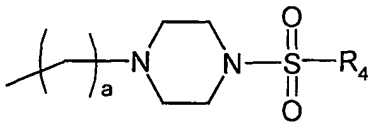
R_2	R_3	R_4
phenyl	isopropyl	
phenyl	isopropyl	
phenyl	ethyl	
cyclohexyl	methyl	$-CH_3$
cyclohexyl	methyl	

The compounds of formula (I) may have at least one asymmetric centre - for example the carbon atom labelled with an asterisk (*) in the compound of formula (I) - and therefore may exist in more than one stereoisomeric form. The invention extends to all such stereoisomeric forms and to mixtures thereof, including racemates. In particular, the invention includes compounds wherein the asterisked carbon atom in formula (I) has the stereochemistry shown in formula (Ia):



(Ia)

wherein R_1, R_2, R_3, R_5, R_6, and R_7 are as defined in relation to formula (I), and X represents the moiety



The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

The term 'alkyl' (unless specified to the contrary) when used alone or when forming part of other groups (such as the 'alkoxy' group) includes straight- or branched-chain alkyl groups containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms, examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl group.

The term 'carbocylic' refers to cycloalkyl and aryl rings.

The term 'cycloalkyl' includes groups having 3 to 12, suitably 4 to 6 ring carbon atoms.

The term 'aryl' includes phenyl and naphthyl, preferably phenyl which unless specified to the contrary optionally comprise up to five, preferably up to three substituents selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

The term 'aromatic heterocyclic group' includes groups comprising aromatic heterocyclic rings containing from 5 to 12 ring atoms, suitably 5 or 6, and comprising up to four hetero-atoms in the or each ring selected from S, O or N.

Composite terms such as 'alkylcarboxy', 'cycloalkylalkyl' and so forth refer to components of a compound which include two interlinked groups, with the group named

latterly in the term being the linking group, so that 'alkylcarboxy' means (alkyl)-COO- whilst 'cycloalkylalkyl' means (cycloalkyl)-(alkyl)-.

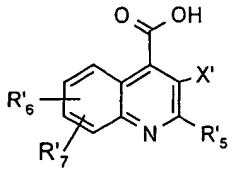
Unless specified to the contrary, suitable substituents for any heterocyclic group includes up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein the term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine or bromine.

It will be understood that unless specified to the contrary, groups and substituents defined herein are unsubstituted.

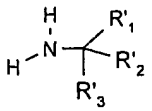
When used herein the term "acyl" includes residues of acids, in particular a residue of a carboxylic acid such as an alkyl- or aryl- carbonyl group.

The invention also provides a process for the preparation of a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



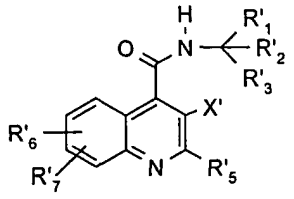
(II)

wherein R'6, R'7, R'5 and X' are R_6, R_7, R_5 and X respectively as hereinbefore defined in relation to formula (I) or (Ia), or a group convertible to R_6, R_7, R_5 and X respectively; with a compound of formula (III):



(III)

wherein R_1', R_2', and R_3' are R_1, R_2, and R_3 as defined for formula (I) or a group or atom convertible to R_1, R_2, and R_3 respectively; to form a compound of formula (Ib):



(Ib)

wherein R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 are as defined above, and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 to R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively as required, to obtain a compound of formula (I);

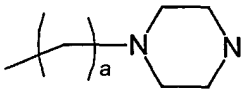
(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

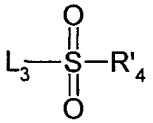
Suitable groups convertible into other groups include protected forms of said groups.

Suitably R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 each represents R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively or a protected form thereof or a group convertible thereto.

In preferred embodiments, X' represents



and said process for preparing a compound of formula (I) further includes the step of reacting said compound (Ib) with a compound of formula



wherein L_3 represents a leaving group for example halogen, preferably chlorine or bromine, and R'_4 represents R_4 or a protected form thereof or a group convertible thereto.

It is favoured if the compound of formula (II) is present as an active derivative.

A suitable active derivative of a compound of formula (II) is a transient activated form of the compound of formula (II) or a derivative wherein the carboxy group of the

compound of formula (II) has been replaced by a different group or atom, for example by an acyl halide, preferably a chloride, or an acylazide or a carboxylic acid anhydride.

Other suitable active derivatives include: a mixed anhydride formed between the carboxyl moiety of the compound of formula (II) and an alkyl chloroformate; an activated ester, such as a cyanomethyl ester, thiophenyl ester, p-nitrophenyl ester, p-nitrothiophenyl ester, 2,4,6-trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-hydroxy-phtalimido ester, N-hydroxypiperidine ester, N-hydroxysuccinimide ester, N-hydroxy benzotriazole ester; alternatively, the carboxy group of the compound of formula (II) may be activated using a carbodiimide or N,N'-carbonyldiimidazole.

The reaction between the compound of formula (II) or the active derivative thereof and the compound of formula (III) is carried out under the appropriate conventional conditions for the particular compounds chosen. Generally, when the compound of formula (II) is present as an active derivative the reaction is carried out using the same solvent and conditions as used to prepare the active derivative, preferably the active derivative is prepared *in situ* prior to forming the compound of formula (Ib) and thereafter the compound of formula (I) or a salt thereof and/or a solvate thereof is prepared.

For example, the reaction between an active derivative of the compound of formula (II) and the compound of formula (III) may be carried out:

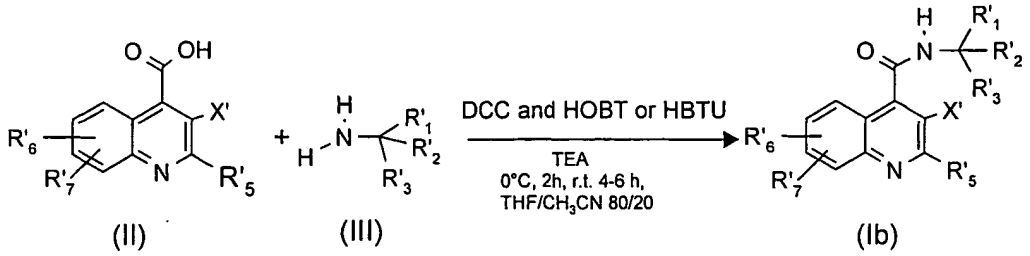
(a) by first preparing an acid chloride and then coupling said chloride with the compound of formula (III) in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C); or

(b) by treating the compound of formula (II) with a compound of formula (III) in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide, preferably in the presence of N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (see *Synthesis,* 453, 1972), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), in an aprotic solvent, such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF), for example a mixture in a volume ratio of from 1:9 to 7:3 (MeCN:THF), at any temperature providing a suitable

rate of formation of the required product, such as a temperature in the range of from -70 to 50°C, preferably in a range of from -10 to 25°C, for example at 0°C.

A preferred reaction is set out in Scheme 1 shown below:

Scheme 1



wherein R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 are as defined above.

It will be appreciated that a compound of formula (Ib) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I) by interconversion of suitable substituents. Thus, certain compounds of formula (I) and (Ib) are useful intermediates in forming other compounds of the present invention.

Accordingly, in a further aspect the invention provides a process for preparing a compound of formula (I), or a salt thereof and/or a solvate thereof, which process comprises converting a compound of the above defined formula (Ib) wherein at least one of R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 is not R_1, R_2, R_3, X, R_5, R_6 or R_7 respectively, thereby to provide a compound of formula (I); and thereafter, as required, carrying out one or more of the following optional steps:

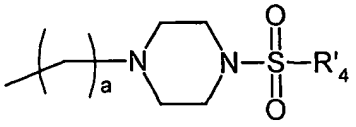
(i) converting a compound of formula (I) into another compound of formula (I); and

(ii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

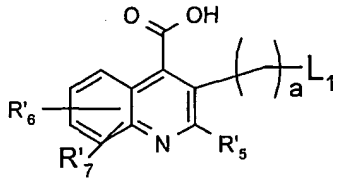
Suitably, in the compound of formula (Ib) the variables R'_1, R'_2, R'_3, X', R'_5, R'_6 and R'_7 are R_1, R_2, R_3, X, R_5, R_6 and R_7 respectively or they are protected forms thereof.

The above mentioned conversions, protections and deprotections are carried out using the appropriate conventional reagents and conditions and are further discussed below.

Where X' represents

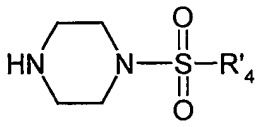


a compound of formula (II) or the corresponding alkyl (such as methyl or ethyl) ester, may conveniently be prepared by reacting a compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester:



(IV)

wherein R'_6, R'_7, R'_5 and a are as defined above and L_1 represents a halogen atom such as a bromine atom, with a compound of formula (V):

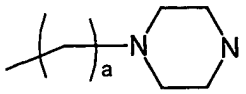


(V)

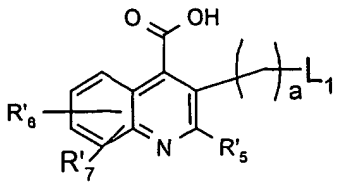
wherein R'_4 is R_4 as defined in relation to formula (I) or a protected form thereof.

Suitably, R'_4 is R_4.

Alternatively, where X' represents

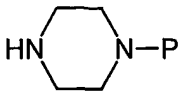


a compound of formula (II) or the corresponding alkyl (such as methyl or ethyl) ester, may conveniently be prepared by reacting a compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester:



(IV)

wherein R'_6, R'_7, R'_5 and a are as defined above and L_1 represents a halogen atom such as a bromine atom, with a compound of formula (V):

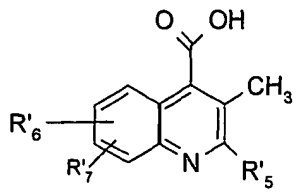


(V)

wherein P is an amine protective group, for example fmoc or benzyl, preferably fmoc, and thereafter removing said protective group. The protective group may be removed by standard methods described in the literature, for example the fmoc residue may be split by action of piperidine at room temperature in a solvent like acetonitrile.

Suitably, reaction between the compounds of formulae (IV) or the corresponding alkyl (such as methyl or ethyl) ester and (V) is carried out under conventional amination conditions, for example when L_1 is a bromine atom then the reaction is conveniently carried out in an aprotic solvent, such as tetrahydrofuran or dimethylformamide at any temperature providing a suitable rate of formation of the required product, usually at ambient temperature; preferably the reaction is carried out in the presence of triethylamine (TEA) or K_2CO_3.

A compound of formula (IV) or the corresponding alkyl (such as methyl or ethyl) ester is prepared by appropriate halogenation of a compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester:



(VI)

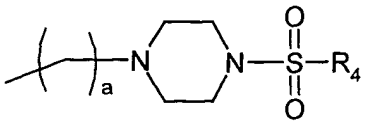
wherein R'_6, R'_7 and R'_5 are as defined above in relation to formula (II).

Suitable halogenation reagents are conventional reagents depending upon the nature of the halogen atom required, for example when L_1 is bromine a preferred halogenation reagent is N-bromosuccinimide (NBS).

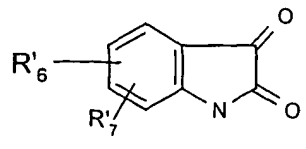
The halogenation of the compound of formula (VI) or the corresponding alkyl (such as methyl or ethyl) ester is carried out under conventional conditions, for example bromination is carried out by treatment with NBS in an inert solvent, such as carbon tetrachloride CCl_4, or 1,2-dichloroethane or CH_3CN, at any temperature providing a suitable rate of formation of the required product, suitably at an elevated temperature such as a temperature in the range of 60°C to 100°C, for example 80°C; preferably the reaction is carried out in the presence of a catalytic amount of benzoyl peroxide.

In the case in which the corresponding alkyl (such as methyl or ethyl) ester of compounds (VI), (IV) and (II) are utilised, an hydrolysis to compound (II) is required before conversion to compound (Ib) in Scheme 1. Such hydrolysis can be carried out under acidic conditions, such 10-36% hydrochloric acid at a temperature in the range between 30 and 100 °C.

A compound of formula (II) wherein X' represents

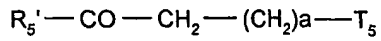


may conveniently be prepared by reacting a compound of formula (VII):



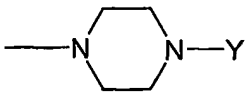
(VII)

wherein R'6 and R'7 are as defined in relation to formula (II), with a compound of formula (VIII):

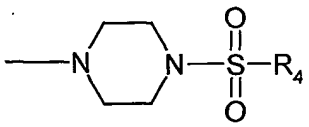


(VIII)

wherein R'5 is as defined in relation to formula (II), and T5 is a group

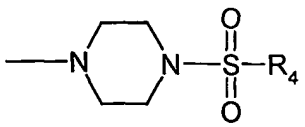


where Y is a protecting group such as a benzyl group, particularly a protecting group which is stable in basic conditions such as a terbutoxycarbonyl group, or a group SO_2R_4 as defined in relation to formula (I) or a protected form thereof or a group convertible thereto, and a is an integer in the range of 1 to 6; and thereafter as required removing any protecting group, for example by dehydrogenation, and/or converting any group T5 to



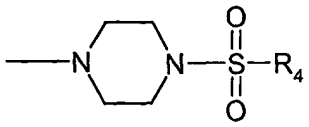
The reaction between the compounds of formula (VII) and (VIII) is conveniently carried out using Pfitzinger reaction conditions (see for example J. Prakt. Chem. 33, 100 (1886), J. Prakt. Chem. 38, 582 (1888), J. Chem. Soc. 106 (1948) and Chem. Rev. 35, 152 (1944)), for example in an alkanolic solvent such as ethanol, at any temperature providing a suitable rate of formation of the required product, but generally at an elevated temperature, such as the reflux temperature of the solvent, and preferably in the presence of a base such as potassium hydroxide or potassium tert-butoxide.

Protected forms of

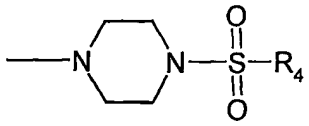


will vary according to the particular nature of the group being protected but will be chosen in accordance with normal chemical practice.

Groups convertible to

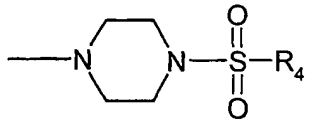


include groups dictated by conventional chemical practice to be required and to be appropriate, depending upon the specific nature of the

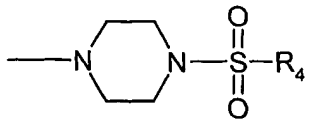


under consideration.

Suitable deprotection methods for deprotecting protected forms of

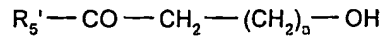


and conversion methods for converting T_5 to



will be those used conventionally in the art depending upon the particular groups under consideration with reference to standard texts such as Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994 and Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; or Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

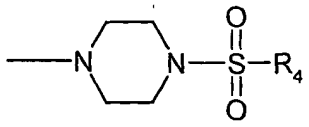
A compound of formula (VIII) is prepared from a compound of formula (IX):



(IX)

wherein R'$_5$ is as defined in relation to formula (II) and a is as defined in relation to formula (VIII), by first halogenating, preferably brominating, or mesylating the compound of formula (IX) and thereafter reacting the halogenation or mesylation product so formed with a compound capable of forming a group T_5 so as to provide the required compound of formula (VII).

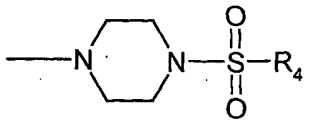
When T_5 is a group



a compound capable of forming a group T_5 is a compound of the above defined formula (V).

The halogenation of the compound of formula (IX) is suitably carried out using a conventional halogenation reagent. Mesylation is conveniently carried out using mesyl chloride in an inert solvent such as methylene dichloride, at a temperature below room temperature, such as 0°C, preferably in the presence of triethylamine.

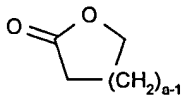
The reaction conditions between the compound of formula (IX) and the compound capable of forming a group T_5 will be those conventional conditions dictated by the specific nature of the reactants, for example when the T_5 required is a group



and the required compound capable of forming a group T_5 is a compound of the above defined formula (V), then the reaction between the halogenation or mesylation product of the compound of formula (IX) and the compound of formula (V) is carried out under analogous conditions to those described for the reaction between the compounds of formulae (IV) and (V).

Other compounds capable of forming a group T_5 will depend upon the particular nature of T_5, but will be those appropriate compounds dictated by conventional chemical practice with reference to standard texts such asChemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; and Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992.

A compound of formula (IX) may be prepared by reacting a compound of formula (X):



(X)

wherein a is as defined in relation to formula (VIII), with a lithium salt of formula (XI):

$$R'_5\ Li \qquad (XI)$$

wherein R'_5 is as defined in relation to formula (II).

The reaction between the compounds of formulae (X) and (XI) can be carried out in an aprotic solvent, such as diethyl-ether at any temperature providing a suitable rate of formation of the required product, usually at a low temperature such as in the range of -10°C to -30°C, for example -20°C.

The compounds of formula (III) are known commercially available compounds or they can be prepared from known compounds by known methods, or methods analogous to those used to prepare known compounds, for example the methods described in Liebigs Ann. der Chemie, (1936), 523, 199.

A chiral compound of formula (III) wherein R_2 is a C_5 or C_7 cycloalkyl group, R_3 is methyl and R_1 is H are described in J. Org. Chem. (1996), 61 (12), 4130-4135. A chiral compound of formula (III) wherein R_2 is phenyl, R_3 is isopropyl and R_1 is H is a known compound described in for example Tetrahedron Lett. (1994), 35(22), 3745-6.

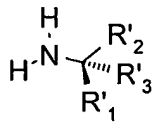
The compounds of formula (V) are known, commercially available compounds or they can be prepared using methods analogous to those used to prepare known compounds; for example the methods described in the Chemistry of the Amino Group, Patais (Ed.), Interscience, New York 1968; Advanced Organic Chemistry, March J, John Wiley & Sons, New York, 1992 ; J. Heterocyclic Chem. (1990), 27, 1559; Synthesis (1975), 135, Bioorg. Med. Chem. Lett. (1997), 7, 555, or Protective Groups in Organic

Synthesis (second edition), Wiley Interscience, (1991) or other methods mentioned herein.

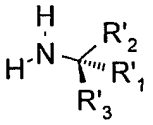
The compounds of formula (VII) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed in J. Org. Chem. 21, 171 (1955); J. Org. Chem. 21, 169 (1955).

The compounds of formula (X) and (XI) are known compounds or they are prepared according to methods used to prepare known compounds for example those disclosed by Krow G. R. in Organic Reactions, Vol 43, page 251, John Wiley & Sons Inc.1994 (for the compounds of formula (X)) and Organometallics in Synthesis, Schlosser M.(Ed), John Wiley & Sons Inc.1994 (for the compounds of formula (XI)).

.As hereinbefore mentioned, the compounds of formula (I) may exist in more than one stereoisomeric form - and the process of the invention may produce racemates as well as enantiomerically pure forms. Accordingly, a pure enantiomer of a compound of formula (I) is obtained by reacting a compound of the above defined formula (II) with an appropriate enantiomerically pure primary amine of formula (IIIa) or (IIIc):

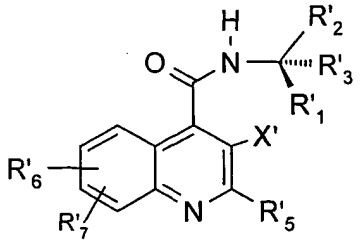


(IIIa)

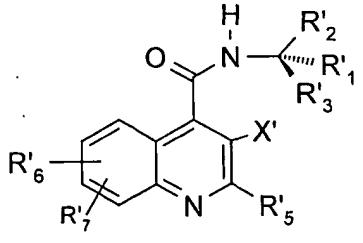


(IIIc)

wherein R'_1, R'_2 and R'_3 are as defined above, to obtain a compound of formula (I'a) or (I'c):



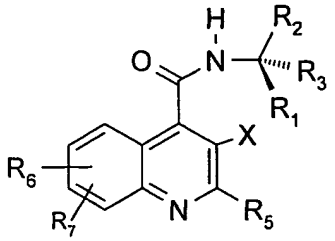
(I'a)



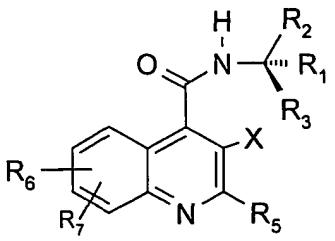
(I'c)

wherein R'_1, R'_2, R'_3, X', R'_5, R'_6, and R'_7 are as defined above.

Compounds of formula (I'a) or (I'c) may subsequently be converted to compounds of formula (Ia) or (Ic) by the methods of conversion mentioned before:



(Ia)



(Ic)

wherein R_1, R_2, R_3, X, R_5, R_6, and R_7 are as defined above.

Suitably, in the above mentioned compounds of formulae (Ia), (Ic), (I'a), (I'c), (IIIa) and (IIIc) R_1 represents hydrogen.

An alternative method for separating optical isomers is to use conventional, fractional separation methods in particular fractional crystallization methods. Thus, a pure enantiomer of a compound of formula (I) is obtained by fractional crystallisation of a diastereomeric salt formed by reaction of the racemic compound of formula (I) with an optically active strong acid resolving agent, such as camphosulphonic acid, , tartaric acid, O,O'-di-p-toluoyltartaric acid or mandelic acid,in an appropriate alcoholic solvent, such as ethanol or methanol, or in a ketonic solvent, such as acetone. The salt formation process should be conducted at a temperature between 20°C and 80°C, preferably at 50°C.

A suitable conversion of one compound of formula (I) into a further compound of formula (I) involves converting one group X into another group X by for example:

(i) converting a ketal into a ketone, by such as mild acidic hydrolysis, using for example dilute hydrochloric acid;

(ii) reducing a ketone to a hydroxyl group by use of a borohydride reducing agent;

(iii) converting a carboxylic ester group into a carboxyl group using basic hydrolysis; and/or

(iv) reducing a carboxylic ester group to a hydroxymethyl group, by use of a borohydride reducing agent.

As indicated above, where necessary, the conversion of any group R'_1, R'_2, R'_3, X', R'_5, R'_6, and R'_7 into R_1, R_2, R_3, X, R_5, R_6, and R_7 which as stated above are

usually protected forms of R_1, R_2, R_3, X, R_5, R_6, or R_7 may be carried out using appropriate conventional conditions such as the appropriate deprotection procedure.

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected and deprotected according to conventional chemical practice, for example as described by Greene, T.W. and Wuts, P.G.M. Protective Groups in Organic Synthesis, John Wiley & Sons Inc. New York, 1991 (Second Edt.) or in Kocienski, P.J. Protecting groups. George Thieme Verlag, New York, 1994.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. Thus, for example suitable hydroxyl protecting groups include benzyl or trialkylsilyl groups.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

As indicated above, the compounds of formula (I) have useful pharmaceutical properties.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

In particular, the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

As mentioned above the Primary conditions include respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, airway hyperreactivity, cough;

inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis and inflammatory pain; neurogenic inflammation or peripheral neuropathy, allergies such as eczema and rhinitis; ophthalmic diseases such as ocular inflammation, conjunctivitis, vernal conjuctivitis and the like; cutaneous diseases, skin disorders and itch, such as cutaneous wheal and flare, contact dermatitis, atopic dermatitis, urticaria and other eczematoid dermatitis; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systhemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), gastro-exophageous reflex disease (GERD); urinary incontinence and disorders of the bladder function; renal disorders; increased blood pressure, proteinuria, coagulopathy and peripheral and cerebral oedema following pre-eclampsia in pregnancies.

As mentioned above, the Secondary conditions include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as AIDS related dementia, senile dementia of the Alzheimer type, Alzheimer's disease, Down's syndrome, Huntington's disease, Parkinson's disease, movement disorders and convulsive disorders (for example epilepsy); demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis and other neuropathological disorders such as diabetic neuropathy, AIDS related neuropathy, chemotherapy-induced neuropathy and neuralgia; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; eating disorders (such as food intake disease); fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of the blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease and pain or nociception, for example, that is attributable to or associated with any of the foregoing conditions especially the transmission of pain in migraine.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an

enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The activity of the compounds of the present invention, as NK_3 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK_3 ligands, [^{125}I]-[Me-Phe^7]-NKB or [^{3}H]-Senktide, to guinea-pig and human NK_3 receptors (Renzetti et al, **1991**, *Neuropeptide, 18*, 104-114; Buell et al, **1992**, *FEBS, 299(1)*, 90-95; Chung et al, **1994**, *Biochem. Biophys. Res. Commun., 198(3)*, 967-972).

The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-[Me-Phe^7]-NKB and [^{3}H]-Senktide specific binding to NK_3 receptor in equilibrium conditions (IC50).

Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of

the present invention show IC_{50} values in the range 0.1-1000 nM. The NK_3-antagonist activity of the compounds of the present invention is determined by their ability to inhibit senktide-induced contraction of the guinea-pig ileum (Maggi et al, **1990**, *Br. J. Pharmacol., 101*, 996-1000) and rabbit isolated iris sphincter muscle (Hall et al., **1991**, *Eur. J. Pharmacol., 199*, 9-14) and human NK_3 receptors-mediated Ca^{++} mobilization (Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Guinea-pig and rabbit *in-vitro* functional assays provide for each compound tested a mean K_B value of 3-8 separate experiments, where K_B is the concentration of the individual compound required to produce a 2-fold rightward shift in the concentration-response curve of senktide. Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilization induced by the agonist NKB. In this assay, the compounds of the present invention behave as antagonists.

The activity of the compounds of the present invention, as NK-2 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK-2 ligands, [^{125}I]-NKA or [^{3}H]-NKA, to human NK-2 receptors (Aharony et al, **1992**, *Neuropeptide, 23*, 121-130).

The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the [^{125}I]-NKA and [^{3}H]-NKA specific binding to NK2 receptor in equilibrium conditions (IC_{50}).

Binding assays provide for each compound tested a mean IC_{50} value of 2-5 separate experiments performed in duplicate or triplicate. The most potent compounds of the present invention show IC_{50} values in the range 0.5-1000 nM, such as 1-1000 nM. The NK-2-antagonist activity of the compounds of the present invention is determined by their ability to inhibit human NK-2 receptor-mediated Ca^{++} mobilization (Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilization induced by the agonist NKA. In this assay, the compounds of the present invention behave as antagonists.

The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed using rodent disease models.

As stated above, the compounds of formula (I) are also considered to be useful as diagnostic tools. Accordingly, the invention includes a compound of formula (I) for use as diagnostic tools for assessing the degree to which neurokinin-3 and neurokinin-2 receptor activity (normal, overactivity or underactivity) is implicated in a patient's symptoms. Such use comprises the use of a compound of formula (I) as an antagonist of said activity, for example including but not restricted to tachykinin agonist-induced inositol phosphate turnover or electrophysiological activation, of a cell sample obtained from a patient. Comparison of such activity in the presence or absence of a compound of formula (I), will disclose the degree of NK-3 and NK-2 receptor involvement in the mediation of agonist effects in that tissue.

The following Descriptions illustrate the preparation of the intermediates, whereas the following Examples illustrate the preparation of the compounds of the invention.

Descriptions and Examples

DESCRIPTION A: **3-Methyl-2-phenyl-quinoline-4-carboxylic acid methyl ester**
30 g (114 mmol) of 3-methyl-2-phenyl-quinoline-4-carboxylic acid (CAS [43071-45-0]) were suspended in 250 ml of dry CH_2Cl_2; 20 ml (230 mmol) of oxalyl chloride dissolved in 120 ml of CH_2Cl_2 were added dropwise and the reaction mixture was stirred at room temperature for 30 min. Two drops of N,N-dimethylformamide (DMF) were added and the reaction was stirred for additional 30 min. The solvent was evaporated *in vacuo* to dryness, the residue was taken up with 100 ml of CH_2Cl_2 and 100 ml of MeOH, dissolved in 400 ml of CH_2Cl_2, were added dropwise. After stirring for 18 h, the solvent was evaporated *in vacuo* to dryness, the residue was taken up with CH_2Cl_2 and washed with 1% $NaHCO_3$; the organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo* to dryness to yield 31.6 g of the title compound as a solid, which was used in the following reaction without further purification.

$C_{18}H_{15}NO_2$
MW 277.31
MP = 73-75°C
IR (KBr) 3441, 3051, 2954, 1731, 1582, 1556 cm^{-1}.

DESCRIPTION B : **3-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester**

10 g (36 mmol) of 3-methyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (compound of Description A) were dissolved in 500 ml of CH_3CN; 13 g (72 mmol) of N-bromosuccinimide were added and the reaction mixture was heated to reflux. After adding 1 g (4.1 mmol) of dibenzoylperoxide, the reaction was refluxed for 24 h; then additional 4 g (22.5 mmol) of N-bromosuccinimide and 0.5 g (2.0 mmol) of dibenzoylperoxide were added and the reaction was refluxed for 4 h. The solvent was evaporated *in vacuo* to dryness to yield 26.1 g of crude methyl 3-bromomethyl-2-phenylquinoline-4-carboxylate (theorical amount, 12.8 g) which was used in the following reaction without further purification.

$C_{18}H_{14}BrNO_2$

MW = 356.23

DESCRIPTION 1 : **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid methyl ester**

6.6 g (18.5 mmol) of crude 3-bromomethyl-2-phenyl-quinoline-4-carboxylic acid methyl ester (compound of Description B) were dissolved, under nitrogen atmosphere, in 100 ml of dry THF. The solution was cooled to 10 °C and 6.8 g (20 mmol) of Fmoc piperazine, dissolved in 50 ml of THF, were added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Salts were filtered off and the filtrate was evaporated *in vacuo* to dryness, taken up with 2 N HCl and washed with EtOAc; the aqueous layer was basified with 10% NaOH and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo* to dryness to obtain a crude material. Flash chromatography on silica gel afforded 7.5 g (yield: 69%) of the title compound.

$C_{37}H_{33}N_3O_4$

MW = 583.68

^1H NMR δ($DMSOd_6$) : 1.99(4H); 3.10(4H); 3.62(2H); 3.97(3H); 4.20(1H); 4.42(2H); 7.18-7.40(4Har); 7.45-7.92(12Har); 8.09(1Har)ppm.

DESCRIPTION 2 : **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid hydrochloride**

7.5 g (13 mmol) of the ester of Description 1 were dissolved in 150 ml of 6 N HCl and refluxed for 1 h. Evaporation to dryness afforded 9.5 g of crude title compound, which was used in the following reaction without further purification.

$C_{36}H_{31}N_3O_4$.HCl

MW = 606.12

^{1}H NMR δ(DMSOd_6) : 2.50(4H); 3.32(4H); 4.22(2H); 4.23(1H); 4.35(2H); 6.50(1Hexch with D_2O); 7.22-7.88(14Har); 7.98(1Har); 8.17(2Har)ppm.

DESCRIPTION 3 : **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide**

5.35 g (8.3 mmol) of crude acid of Description 2 were dissolved in 100 ml of dry THF; 1.7 ml (12.5 mmol) of triethylamine (TEA) and 4.1 g (10.79 mmol) of O-benzotriazol-1-yl-N,N,N',N'-tetramethyluroniumhexafluoro-phosphate (HBTU) were added and the reaction mixture was cooled at 0 °C. 1.7 ml (12.5 mmol) of (S)-1-phenyl-propylamine, dissolved in 40 ml of dry CH_2Cl_2, were added dropwise and the reaction mixture was stirred at room temperature for 24 h and at 50 °C for 2 h. The solvent was evaporated *in vacuo* to dryness and the residue was taken up with EtOAc and washed with H_2O, 1 N NaOH and brine, dried over Na_2SO_4 and evaporated to dryness . Flash chromatography on silica gel afforded 3.2 g (56%) of the title compound.

$C_{45}H_{42}N_4O_3$

MW = 686.86

^{1}H NMR δ(DMSOd_6) : 0.94(3H); 1.40-2.18(6H); 2.57-3.13(4H); 3.50(2H); 4.21(1H); 4.34(2H); 5.08(1H); 7.09-7.98(21Har); 8.03(1Har): 9.12(1Hexch with D_2O)ppm.

DESCRIPTION 4 : **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**

4.75 g (8.3 mmol) of crude acid of Description 2 were condensed on 1.65 ml (11 mmol) of (S)-1-cyclohexyl-ethylamine following the procedure of Description 3 affording, after flash chromatography on silica gel, 2.2 g (yield 43.9%) of the title compound.

$C_{44}H_{46}N_4O_3$

MW = 678.87

^{1}H NMR δ(DMSOd_6) : 0.95(3H); 1.68-4.00(21H); 2.60(3H); 5.08(1H); 7.22-8.24(13Har); 8.11(1Har); 9.32(1Hexch with D2O); 10.82(2Hexch with D_2O)ppm.

DESCRIPTION 5 : **2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-phenyl-propyl)-amide**

2.75 g (41 mmol) of the Fmoc protected derivative of Description 3 was reacted with 1.0 ml of piperidine in 100 ml acetonitrile, at room temperature for one night. The reaction mixture is concentrated to dryness and the residue was purified by flash chromatography on silicagel, affording 1.14 g (yield 60%) of the title compound.

$C_{30}H_{32}N_4O$

MW = 464.61

^{1}H NMR δ(DMSOd_6) : 0.94(3H); 1.57-2.08(6H); 2.31(4H); 3.36(2H and 1Hexch with D_2O); 5.07(1H); 7.13-7.94(13Har); 8.01(1Har); 9.17(1Hexch with D_2O)ppm.

DESCRIPTION 6 : **3-(4-Fmoc-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide**

6.95 g (10.8 mmol) of crude acid of Description 2 were condensed on 2 g (13.5 mmol) of (S)-2-methyl-1-phenyl propylamine following the procedure of Description 3 affording, after flash chromatography on silica gel, 5.4 g (yield 71%) of the title compound.

$C_{46}H_{44}N_4O_3$

MW = 700.86

^{1}H NMR δ($CDCl_3$) : 0.96(3H); 1.18(3H); 1.56-2.98(4H); 2.28(1H); 3.04(4H); 3.53(2H); 4.20(1H); 4.35(2H); 5.17(1H); 7.18-7.63(18Har); 7.74(3Har); 7.97(1Hexch with D_2O); 8.14(1Har)ppm.

DESCRIPTION 7 : **2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide**

5.4 g (7.7 mmol) of the Fmoc derivative of Description 6 was reacted with 1.25 ml of piperidine in 200 ml acetonitrile, at room temperature for one night. The reaction mixture was concentrated to dryness and the residue was purified by flash chromatography on silicagel (eluant: $CH_2Cl_2/CH_3OH/NH_4OH$; 90/10/2), affording 2.55 g (yield 69.3%) of the title compound.

$C_{31}H_{34}N_4O$
MW = 478.64
^1H NMR δ($DMSOd_6$) : 0.79(3H); 1.06(3H); 1.49-2.55(9H); 3.45(2H and 1Hexch with D2O); 4.88(1H); 7.12-8.10(14Har); 9.16(1Hexch with D_2O)ppm.

DESCRIPTION 8 : **2-Phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-1-cyclohexyl-ethyl)-amide**
Synthesised starting from the compound of Description 4 and following the procedure of Description 5.

$C_{29}H_{36}N_4O$
MW = 456.63

DESCRIPTION 9: : **(S)-N-(1-Phenylpropyl)-3-(4-ethenesulfonyl-piperazin-1-ylmethyl)-2-phenylquinoline-4-carboxyamide**
2.8 g (6.13 mmol) of the compound of Description 5 and 0.85 g (6.13 mmol) of K_2CO_3 were suspended in 20 ml of CH_2Cl_2 and the mixture was cooled to 0°C. 1 g (6.13 mmol) of 2-chloroethylsulphonylchloride, dissolved in 5 ml of CH_2Cl_2, were added dropwise and the mixture was stirred at room temperature for 2 hours. 10 ml of H_2O were added and the slurry was stirred for additional 10 minutes. The acqueous phase was separated and extracted three times with CH_2Cl_2. The organic phases, collected together were washed with water, dried over Na_2SO_4, filtered and evaporated *in vacuo* to dryness to yield 1.2 g of a yellow powder. The crude comound was purified by flash chromatography on silicagel (eluent: hexane/EtOAc; 1/1), affording 0.15 g of the title compound.

$C_{32}H_{34}N_4O_3S$

MW = 554.654

IR: (KBr) 3286, 3059, 2933, 1638, 1534, 1492, 1454, 1158, 952, 763, 701 cm-1

EXAMPLE 1 : **3-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazine-1-sulfonyl}-propionic acid methyl ester**

A suspension of 1.2 g (2.5 mmol) of 2-phenyl-3-piperazin-1-ylmethyl-quinoline-4-carboxylic acid ((S)-2-methyl-1-phenyl-propyl)-amide (compound of Description 7) in 20 ml of acetonitrile was reacted with 0.513 g (2.75 mmol) of beta carbomethoxyethanesulfonyl chloride and 482 ul (2.75 mmol) of diisopropylethylamine. The reaction mixture was stirred at room temperature for 15 h followed by 3 h at 50°C. The solvent was concentrated and the residue taken up in CH_2Cl_2. The un-reacted starting amine (0.46 g) was filtered off and the solution was washed twice with water, dried over $MgSO_4$ and concentrated.

The crude compound was purified by flash chromatography over 45 g silica gel (eluent : CH_2Cl_2/MeOH : 99/1) to afford 0.48 g of the title compounds as a cream solid.

$C_{35}H_{40}N_4O_5S$

MW = 628.790

M.P. = 105-107

EXAMPLE 2 : **3-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazine-1-sulfonyl}-propionic acid.**

A mixture of 0.43 g (6.8 mmol) of 3-{4-[4-((S)-2-methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazine-1-sulfonyl}-propionic acid methyl ester (compound of Example 1), 4 mml of ethanol and 0.72 ml of 1N aqueous sodium hydroxide were stirred at room temperature for 1 h. The solvent was concentrated and the residue neutralised by a few drops of acetic acid and purified by flash chromatography over 45 g of silicagel (eluent : CH_2Cl_2/MeOH : 95/5). The desired fractions were pooled, concentrated and the residue crystallised in diisoprpyl ether. The compound obtained thereafter being impure the same process (chromatography + crystallisation) was applied again affording now 60 mg of the title compound as light yellow crystals.

$C_{34}H_{38}N_4O_5S$

MW = 614.763

M.P. = 150-5°C.

EXAMPLE 3 : **(-)-(S)-N-(1-Phenylpropyl)-3-[(2-N',N'-diethylamino-1-ethyl)sulphonyl]-2-**

phenylquinoline-4-carboxamide

0.1 g (0.18 mmol) of compound of Description 9 and 5 ml (48 mmol) of diethylamine were dissolved in 10 ml of CH_2Cl_2 and the solution was stirred at room temperature for 15 days.

The solvent was evaporated *in vacuo* to dryness, the residue was dissolved in AcOEt, washed with water and dried over Na_2SO_4. After concentration of the solvent the residue was purified by flash chromatography (eluent, hexane/AcOEt : 9/1) affording 0.067 g of the title compound as yellow powder.

$C_{36}H_{45}N_5O_3S$

MW = 627.79

M.P. : 93-97°C.

IR : (KBr) 3296, 3059, 2968, 1658, 1531, 1153, 955, 764, 702 cm-1

EXAMPLE 4 : **(S)-N-(1-cyclohexylethyl)-3-(4-methanesulfonylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxyamide**

0.3 g (0.66 mmol)of (S)-N-(1-cyclohexylethyl)-3-[4-piperazin-1-yl]methyl-2-phenylquinoline-4-carboxamide (compound of description 8), 0.082 g (0.7 mmol)of methanesulfonyl chloride and 0.1 ml (0.7 mmol) of TEA were dissolved in 20 ml of THF. The solution was stirred at room temperature for 18 hours then the solvent was evaporated *in vacuo* to dryness. The residue was dissolved in AcOEt. The organic phase was washed with 1N NaOH solution and with water, then dried over Na_2SO_4. After concentration of the solvent the residue was purified by flash chromatography (eluent, hexane/AcOEt : 1/1) affording 0.27 g (78%) of the title compound as white powder.

$C_{30}\ H_{38}\ N_4\ O_3\ S$

MW: 534.72

M.P.: 138-140°C

IR: (nujol) 3283, 1634, 1537, 1455 cm-1

EXAMPLE 5 : **((S)-1-cyclohexylethyl)-3-(4-benzenesulfonylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxyamide**

0.3 g (0.6 mmol) of (S)-N-(1-cyclohexylethyl)-3-[4-piperazin-1-yl]methyl-2-phenylquinoline-4-carboxamide (compound of description 8), 0.1 ml (0.7 mmol) of benzenesulfonyl chloride and 0.1 ml (0.7 mmol) of TEA were dissolved in 20 ml of THF. The solution was stirred at room temperature for 18 hours then the solvent was evaporated *in vacuo* to dryness. The residue was dissolved in AcOEt. The organic phase was washed with 1N NaOH solution and with water, then dried over Na_2SO_4. After concentration of the solvent the residue was purified by flash chromatography (eluent, hexane/AcOEt : 2/1) affording 0.150 g (38%) of the title compound as white powder.

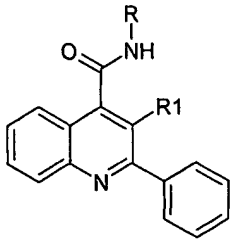
$C_{35}\ H_{40}\ N_4\ O_3\ S$

MW: 596.79

M.P.: 208-210 °C

IR: (nujol) 1626, 1553, 1455, 1355 cm-1

TABLE 1



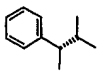
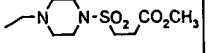
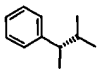
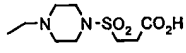
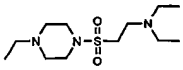
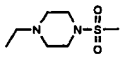
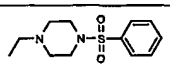
Ex.	R	R_1	Molecular Formula	Molecular Weight	Melting Point (°C)	$[a]_D^{20}$ (c=0.5, MeOH)
1			$C_{35}H_{40}N_4O_5S$	628.790	105-107	
2			$C_{34}H_{38}N_4O_5S$	614.763	150-155	
3			$C_{36}H_{45}N_5O_3S$	627.79	93-97	-54.05 (c=0.26)
4			$C_{30}H_{38}N_4O_3S$	534.72	138-140	+13.43 (c= 0.1)
5			$C_{35}H_{40}N_4O_3S$	596.79	208-210	+13.3 (c= 0.1)

TABLE 2

^{1}H NMR data of compounds of Examples of Table 1

Ex.	^{1}H NMR (Solvent) *delta* ppm
1	($CDCl_3$) δ : 0.94(d,3H); 1.17(d,3H); 1.93(m,4H); 2.24(m,1H); 2.73(t,2H); 2.80(m,4H); 3.09(t,2H); 3.53(s,2H); 3.53(s,3H); 5.13(m,1H); 6.90(d,1Har); 7.27-7.64(m,11Har); 7.74(td,1Har); 7.89(br,1H); 8.14(dd,1Har)ppm
2	(CDCl3) δ : 0.91(d,3H); 1.15(d,3H); 1.91(m,4H); 2.20(m,1H); 2.71(t,2H); 2.82(m,4H); 3.10(t,2H); 3.27(br,1H); 3.51(s,2H); 5.10(m,1H); 6.88(d,1Har); 7.25-7.63(m,11Har); 7.73(t,1Har); 7.93(br,1H); 8.13(d,1Har)ppm.
3	(DMSO) (343 K); 8.87(d, 1H); 8.02(d, 1H); 7.76(dd, 1H); 7.71(m, 1H); 7.60-7.42(m, 8H); 7.38(dd, 2H); 7.28(dd, 1H); 5.10(dt, 1H); 3.54(s br, 2H); 3.00(m, 2H); 2.81(m, 4H); 2.74(m, 2H); 2.48(q, 4H);2.04(m, 4H); 1.98-1.76(m, 2H); 0.98(t, 6H); 0.97(t, 3H).
4	(CDCl3): 8.15(d, 1H); 7.98(d, 1H); 7.74(dd, 1H); 7.60(dd, 1H); 7.52-7.41(m, 5H); 6.56(s br, 1H); 4.26(dt, 1H); 3.76(s, 2H); 2.98(m, 4H); 2.68(s, 3H); 2.31(m, 4H); 1.98-1.66(m, 5H); 1.47(m, 1H); 1.35-1.02(m, 5H);1.29(d, 1H)
5	(DMSO): 8.20(d br, 1H); 7.99(d, 1H); 7.82(d, 1H); 7.78-7.58(m, 7H); 7.41(m, 2H); 7.31(m, 3H); 3.97(dt, 1H); 3.62(s, 2H); 2.66(m, 4H); 2.18(m, 4H);1.83-1.60(m, 5H); 1.46(m, 1H); 1.31-1.02(m,5H); 1.13(d, 3H)

TABLE 3
Mass Spectra data of compounds of Examples of Table 1

Ex.	m/z (ESI POS; AQA ; solvent: methanol/ spray 3 kV / skimmer: 20 V/ probe 135 C)	m/z (EI; TSQ 700; source 180 °C;70 eV; 200 uA)
1		
2		
3	628 (MH+)	
4		534 (M+.); 455; 407; 380; 372; 328; 316; 300; 261; 246; 217
5		442; 372; 370; 328; 316; 300; 261; 217; 140

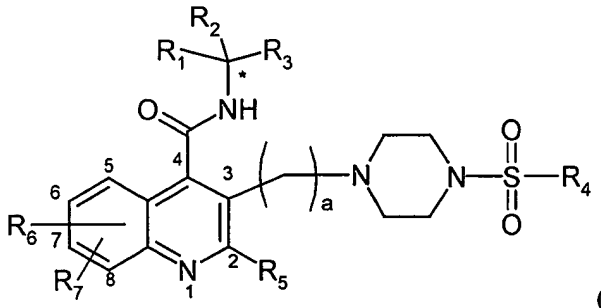
TABLE 4

Chemical names of parent compounds of Examples of Table 1 (names generated by Beilstein's Autonom)

Example	Chemical name
1	3-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-sulfonyl}-propionic acid methyl ester
2	3-{4-[4-((S)-2-Methyl-1-phenyl-propylcarbamoyl)-2-phenyl-quinolin-3-ylmethyl]-piperazin-1-sulfonyl}-propionic acid
3	(-)-(S)-N-(1-Phenylpropyl)-3-[(2-N',N'-diethylamino-1-ethyl)sulphonyl]-2-phenylquinoline-4-carboxamide
4	(S)-N-(1-cyclohexylethyl)-3-(4-methanesulfonylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxyamide
5	((S)-1-cyclohexyl-ethyl)-3-(4-Benzenesulfonylpiperazin-1-ylmethyl)-2-phenylquinoline-4-carboxyamide

CLAIMS

1 A compound of formula (I) below or a pharmaceutically acceptable salt or hydrate thereof:



(I)

(I)

wherein:

R_1 is H or C_{1-6} alkyl;

R_2 is aryl or C_{3-7} cycloalkyl or heteroaryl;

R_3 is H or C_{1-3} alkyl, optionally substituted by one or more fluorines;

R_4 is R_8R_9;

R_8 is a single bond, C_{1-6} alkyl, or aryl;

R_9 is H, COO R_{10}, or N $R_{11}R_{12}$;

R_{10} is H or C_{1-6} alkyl;

R_{11} and R_{12} are independently selected from H and C_{1-6} alkyl, or are joined to form a 5-7 membered heterocyclic ring;

R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, aryl, or a single or fused ring aromatic heterocyclic group;

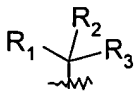
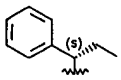
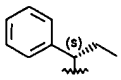
R_6 represents H or up to three substituents independently selected from the list consisting of: C_{1-6} alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, amino or mono- or di-C_{1-6} alkylamino;

R_7 is H or halo;

a is 1-6; and

any of R_2, R_5, R_8, R_{10}, R_{11} and R_{12} may optionally be substituted one or more times by halo, hydroxy, amino, cyano, nitro, carboxy or oxo;

subject to the proviso that said compound is not a compound of formula (I) wherein R_7 represents H, R_6 represents H, R_5 represents phenyl, a is 1, and R_1, R_2, R_3 and R_4 are one of the following combinations:

	R_4
	$-NH_2$
	

2 A compound as claimed in claim 1, wherein R_8 is methyl, ethyl or phenyl.

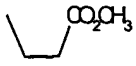
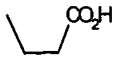
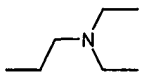
3 A compound as claimed in claim 1 or claim 2, wherein R_9 is H.

4 A compound as claimed in claim 1 or claim 2, wherein R_9 is $COOR_{10}$ and R_{10} is H or methyl or ethyl.

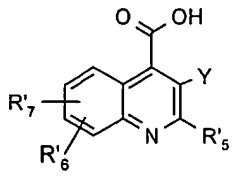
5 A compound as claimed in claim 1 or claim 2, wherein wherein R_9 is $NR_{11}R_{12}$, and R_{11} and/or R_{12} is methyl, ethyl or propyl.

6 A compound as claimed in claim 5, wherein R_{11} and R_{12} are the same one of ethyl or propyl.

7 A compound as claimed in claim 1, wherein a is 1, R_6 is H, R_1 is H, R_5 is unsubstituted phenyl, R_7 is hydrogen, and R_2, R_3 and R_4 are selected from the following combinations:

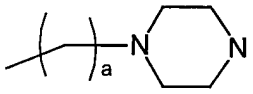
R_2	R_3	R_4
phenyl	isopropyl	
phenyl	isopropyl	
phenyl	ethyl	
cyclohexyl	methyl	$-CH_3$
cyclohexyl	methyl	

8 A process for the preparation of a compound of formula (I) according to any of claims 1-7, or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II) or an active derivative thereof:



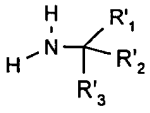
(II)

wherein R'5, R'6, and R'7 are R_5, R_6, and R_7 respectively as defined in relation to formula (I) or a group convertible to R_5, R_6, and R_7 respectively, and Y' is a group of formula (Y) or a protected form thereof:



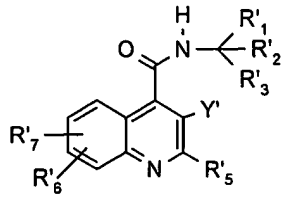
(Y)

with a compound of formula (III):



(III)

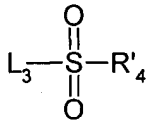
wherein R'1, R'2 and R'3 are R_1, R_2 and R_3 as defined for formula (I) or a group or atom convertible to R_1, R_2 and R_3 respectively; to form a compound of formula (Ib):



(Ib)

wherein R'_1, R'_2, R'_3, R'_5, R'_6, R'_7 and Y' are as defined above;

reacting said compound (Ib) with a compound of formula



wherein L_3 represents a leaving group for example halogen, preferably chlorine or bromine, and R'_4 represents R_4 or a protected form thereof or a group convertible thereto;

and thereafter carrying out one or more of the following optional steps:

(i) converting any one of R'_1, R'_2, R'_3, R'_4, R'_5, R'_6, and R'_7 to R_1, R_2, R_3, R_4, R_5, R_6, and R_7 respectively as required, to obtain a compound of formula (I);

(ii) converting a compound of formula (I) into another compound of formula (I); and

(iii) preparing a salt of the compound of formula (I) and/or a solvate thereof.

9 A pharmaceutical composition comprising a compound of formula (I) according to any of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

10 A compound of formula (I) according to any of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

11 A compound of formula (I) according to any of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, for the treatment or prophylaxis of the Primary and Secondary Conditions.

12 Use of a compound of formula (I) according to any of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Conditions.

13 A method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective, non-toxic pharmaceutically acceptable amount of a compound of formula (I) according to any of claims 1-7 or a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

Inte[illegible]l Application No
PCT/EP 01/13141

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/52 A61K31/47 A61K31/4709 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 31037 A (NADLER GUY MARGUERITE MARIE G ;MORVAN MARCEL (FR); SMITHKLINE BEEC) 2 June 2000 (2000-06-02) cited in the application claim 13; examples 90,91	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2002	08/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[illegible]al Application No
PCT/EP 01/13141

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0031037 A	02-06-2000	AU 1777000 A	13-06-2000
		BR 9915475 A	18-12-2001
		WO 0031037 A1	02-06-2000
		EP 1131295 A1	12-09-2001
		NO 20012473 A	18-07-2001